Mortality risk among hemodialysis patients receiving different vitamin D analogs

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To the Editor: Tentori *et al.*[1] reported a 20% increased risk of mortality in dialysis patients who were not taking intravenous vitamin D compared to those who received vitamin D, confirming studies showing a survival benefit in patients administered vitamin D.[2–4] However, Tentori *et al.* claim there was no differences in mortality risk when comparing the use of calcitriol (1α,25-dihydroxyvitamin D_3) with doxercalciferol (1α-hydroxyvitamin D_2) and paricalcitol (19-nor-1α,25-dihydroxyvitamin D_2). Unfortunately, there are significant limitations with their analyses, and subsequent conclusions. The authors have taken liberty in their claim of 'equivalency' between doxercalciferol and paricalcitol and in their comparison to previous studies that employed larger databases and longer treatment periods.[2–4]

It is unclear if the authors understand the differences between the various vitamin D compounds. Although both paricalcitol and doxercalciferol are D_2, whereas calcitriol is a D_3 compound, the major differentiating factor in the activation of the vitamin D receptor (VDR) is that paricalcitol has a modification in the A ring. In fact, doxercalciferol is an inactive pro-hormone that has to be converted by the liver to its active form (1α,25-dihydroxyvitamin D_2) and it is unclear if there are differences in the activation of the VDR by 1α,25-D_3 or 1α,25-D_2. Thus, it is misleading when the authors equate paricalcitol and doxercalciferol by referring to them collectively as D_2 compounds.

Important limitations of this study include the relatively small number of patients and the fact that the treatments were not simultaneous but sequential and short in duration. There were 7731 patients who received vitamin D at any time and the median observation period was less than 10 months. Patients who received calcitriol started sooner after initiating dialysis, were not dosed according to KDOQI guidelines and were started on therapy earlier in the study period than those receiving other compounds, whereas those who received doxercalciferol had the shortest follow-up and were started on therapy later in the study period. Moreover, only about 50% of the treated patients received vitamin D for more than 6 months. The high rate of censoring was largely due to patients being switched from one D compound to another (38%). It is likely that the study was underpowered to show a 12–16% survival difference between calcitriol and paricalcitol as was demonstrated by Teng *et al.* after evaluation of 67 399 patients.[2]

On the basis of these limitations, the authors should acknowledge that they were unable to show survival differences among the vitamin D treatment groups in large part because the study was underpowered and the design was not appropriate to make a statement of equivalence. This would be a fairer interpretation of their data than the inappropriate claim that the major finding of the study was the lack of a survival difference between paricalcitol and doxercalciferol. In addition to the impact on patient care, there is an enormous financial stake associated with the use of these compounds. Thus, before coming to conclusions regarding the effect of vitamin D in general and the relative effect of different compounds in particular, appropriately designed and powered studies are required to determine the best practice for reducing mortality associated with chronic kidney disease.

1. Tentori F, Hunt WC, Stidley CA *et al.* Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int* 2006; **70**: 1858–1865.
2. Teng M, Wolf M, Lowrie E *et al.* Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 2003; **349**: 446–456.
3. Teng M, Wolf M, Ofsthun MN *et al.* Activated injectable vitamin D and hemodialysis survival: a historical cohort study. *J Am Soc Nephrol* 2005; **16**: 1115–1125.
4. Kalantar-Zadeh K, Kuwae N, Regidor DL *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006; **70**: 771–780.

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Response to 'Mortality risk among hemodialysis patients receiving different vitamin D analogs'

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We appreciate Dr Sprague's letter[1] to our article.[2] Doxercalciferol undergoes hepatic conversion to its active form (1,25-dihydroxyvitamin D_2), but once activated, it is a vitamin D_2 analog.

Dialysis Clinic Inc. (DCI) is a large not-for-profit provider. Procedural differences between DCI and for-profit providers may influence clinical outcomes. The use of an incident versus a prevalent cohort reduced our sample size and the impact of potential confounders. The crude mortality rate (deaths/100 patient years, 95% confidence interval (CI)) was higher among patients receiving calcitriol (19.6, 18.2–21.1) versus paricalcitol (15.3, 13.6–16.9) ($P<0.0001$) or doxercalciferol (15.4, 13.6–17.1) ($P=0.0003$). However, in our Cox models, administration of paricalcitol and doxercalciferol versus calcitriol was associated with a survival benefit only in the unadjusted model and the model adjusted for demographics, reflecting our relatively small sample. Never-